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Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial

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Summary

Background Treatments for open-angle glaucoma aim to prevent vision loss through lowering of intraocular pressure, but to our knowledge no placebo-controlled trials have assessed visual function preservation, and the observation periods of previous (unmasked) trials have typically been at least 5 years. We assessed vision preservation in patients given latanoprost compared with those given placebo.

Methods In this randomised, triple-masked, placebo-controlled trial, we enrolled patients with newly diagnosed open-angle glaucoma at ten UK centres (tertiary referral centres, teaching hospitals, and district general hospitals). Eligible patients were randomly allocated (1:1) with a website-generated randomisation schedule, stratified by centre and with a permuted block design, to receive either latanoprost 0.005% (intervention group) or placebo (control group) eye drops. Drops were administered from identical bottles, once a day, to both eyes. The primary outcome was time to visual field deterioration within 24 months. Analyses were done in all individuals with follow-up data. The Data and Safety Monitoring Committee (DSMC) recommended stopping the trial on Jan 6, 2011 (last patient visit July, 2011), after an interim analysis, and suggested a change in primary outcome from the difference in proportions of patients with incident progression between groups to time to visual field deterioration within 24 months. This trial is registered, number ISRCTN96423140.

Findings We enrolled 516 individuals between Dec 1, 2006, and March 16, 2010. Baseline mean intraocular pressure was 19.6 mm Hg (SD 4.6) in 258 patients in the latanoprost group and 20.1 mm Hg (4.8) in 258 controls. At 24 months, mean reduction in intraocular pressure was 3.8 mm Hg (4.0) in 231 patients assessed in the latanoprost group and 0.9 mm Hg (3.8) in 230 patients assessed in the placebo group. Visual field preservation was significantly longer in the latanoprost group than in the placebo group: adjusted hazard ratio (HR) 0.44 (95% CI 0.28–0.69; $p=0.0003$). We noted 18 serious adverse events, none attributable to the study drug.

Interpretation This is the first randomised placebo-controlled trial to show preservation of the visual field with an intraocular-pressure-lowering drug in patients with open-angle glaucoma. The study design enabled significant differences in vision to be assessed in a relatively short observation period.

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Introduction

Open-angle glaucoma is a chronic progressive optic neuropathy that causes a loss of vision, predominantly affecting the mid-peripheral visual field at first and later damaging central vision as the disease progresses; although increasingly evidence suggests unrecognised damage to central vision early in the disease course. Glaucomatous vision loss is associated with restricted mobility,¹ falls and motor vehicle accidents,² and is the leading cause of irreversible blindness worldwide and the second major cause for blind registration in the UK.^{3,4} The prevalence of open-angle glaucoma increases exponentially with age and the level of intraocular pressure.⁵ Drugs to reduce intraocular pressure have been used for decades to slow or halt progressive vision loss in patients with open-angle glaucoma, yet there has been no placebo-controlled trial to assess vision

preservation with this treatment. For most patients, the first-choice drug is a prostaglandin analogue,⁶ although a recent Cochrane review of medical interventions for glaucoma reported no published evidence for a protective effect on vision.⁷ The United Kingdom Glaucoma Treatment Study (UKGTS) is the first placebo-controlled trial to assess the effect of intraocular-lowering treatment on vision preservation.

Previous trials to assess intraocular-lowering treatment on vision preservation in open-angle glaucoma have compared medical treatment with no treatment,⁸ combined medical and laser therapy with no treatment (the Early Manifest Glaucoma Trial⁹ [EMGT] in 2002), one medical treatment with another,^{10,11} medical, laser, or surgical intraocular pressure reduction with no treatment,¹² medical with laser and surgical pressure reduction,¹³ initial medical with surgical pressure

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reduction,^{14,15} and different laser and surgical sequences in addition to medical treatment (the Advanced Glaucoma Intervention Study¹⁶ [AGIS]). To our knowledge, no study has been done in patients with open-angle glaucoma to assess the vision-preserving efficacy of one drug in a placebo-controlled trial.

The observation period for trials of visual field preservation in patients with open-angle glaucoma has typically been 5 years or longer,^{9,12,15,16} with the shortest trial lasting 30 months.¹¹ Long trial duration hinders the assessment of new interventions to prevent vision loss and increases the cost of drug development, which, in turn, reduces the likelihood of new treatments being made available for patient benefit. Therefore, the design of UKGTS incorporated approaches for the measurement of outcomes that have potential to shorten study design, including repeated tests on visits (clustering) at the beginning and end of the observation period and imaging the retinal nerve fibre layer and optic nerve head. Both the clustering and inclusion of imaging can increase the precision of estimates of the rate (speed) of change.^{17,18} We aimed to assess the effect of the prostaglandin analogue latanoprost on the visual field preservation of patients with open-angle glaucoma in a comparatively short trial.

Methods

Study design and participants

The UKGTS is a randomised, multicentre, triple-masked, parallel-group, placebo-controlled trial, undertaken in ten participating centres (tertiary referral centres, teaching hospitals, and district general hospitals) throughout the UK. The study design and baseline characteristics of UKGTS participants have been published previously.^{19,20}

We consecutively identified participants with newly diagnosed, untreated open-angle glaucoma. Our eligibility criteria were closely modelled on those from the EMGT²¹ to allow comparison and meta-analysis. Open-angle glaucoma was defined as the presence of glaucomatous visual field defects in at least one eye with corresponding damage to the optic nerve head (see supplemental procedures in the appendix) and an open iridocorneal drainage angle on gonioscopy. We allowed patients with primary open-angle glaucoma and pseudoexfoliation glaucoma, but not pigment dispersion glaucoma. Exclusion criteria included advanced glaucoma (visual field mean deviation worse than -10 dB in the better eye or -16 dB in the worse eye), mean baseline intraocular pressure of 30 mm Hg or higher, Snellen visual acuity worse than 6/12, and poor image quality (>40 µm mean pixel height standard deviation) with the Heidelberg retina tomograph (Heidelberg Engineering, Heidelberg, Germany). After the Moorfields Eye Hospital Reading Centre confirmed eligibility and the patient gave informed consent, the Moorfields Clinical Trials Unit assigned a study identification number.

The study was undertaken in accordance with good clinical practice guidelines and adhered to the Declaration of Helsinki. The trial was approved by the Moorfields and Whittington Research Ethics Committee on June 1, 2006 (reference 09/H0721/56). All patients provided written informed consent before screening investigations. An independent Data and Safety Monitoring Committee (DSMC) was appointed by the trial steering committee. The trial manager monitored adverse events, which were reported immediately to the operational DSMC at Moorfields Eye Hospital. Serious adverse events were reported to the Medicines and Healthcare Products Regulatory Agency.

Randomisation and masking

We randomly allocated participants (1:1) to either latanoprost 0.005% or latanoprost vehicle eye drops (placebo) alone once a day in both eyes. Patients were enrolled by clinicians at each site; once eligibility was confirmed by the reading centre, the Moorfields Clinical Trials Unit assigned patients the next available study identification number. We did randomisation in permuted blocks of varying sizes (block sizes range from 4 to 10), stratified by participating centre. The randomisation schedule, drawn up by the research and development statisticians at Moorfields Eye Hospital on a randomisation website, was sent to the Pharmaceutical Manufacturing Unit, which labelled the bottles with the participant study identification number only. Latanoprost and placebo eye drops were provided in identical-looking bottles. Participants, clinicians, and assessors of the primary outcome were masked to the treatment allocation and clinicians were encouraged not to tell the participants their intraocular pressure measurements.

Outcomes

After the funding decision and before trial initiation, the primary endpoint was changed from the one used in the EMGT—at least three test locations showing significant deterioration at the $p < 0.05$ level in three consecutive 30-2 visual fields—to at least three visual field locations worse than baseline at the 5% levels in two consecutive reliable visual fields and at least three visual field locations worse than baseline at the 5% levels in the two subsequent consecutive reliable visual fields; the locations identified in the first and second pair were not required to be identical. This change was made because the visual field test in the UKGTS was smaller in extent (24-2), and therefore fewer locations were tested than in the EMGT. Time to progression was defined as time from baseline to the fourth visual field that confirmed progression. The primary endpoint was assessed on the day of each visit and then verified by the Reading Centre.

After the publication of the National Institute for Health and Care Excellence Guideline *Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension*,⁶ the independent DSMC requested an

For the randomisation website see <http://www.randomization.com>

See Online for appendix

(unplanned) interim analysis on Jan 6, 2011, based on time-to-event. The Steering Committee therefore formally adopted time-to-event for the primary outcome. On the basis of the interim analysis, the DSMC requested an early termination of the trial and patients were scheduled for exit visits over the subsequent 3 months.

We give survival data of differences in time from baseline to the event of confirmed deterioration between treatment groups. Additional endpoints were intraocular pressure higher than 35 mm Hg on two successive occasions (safety endpoint) and visual acuity reduction to less than 6/18 (non-glaucomatous vision change endpoint). We also report the original primary endpoint—proportion of patients with deterioration at 24 months in each group. Secondary outcomes included visual field deterioration rate (speed), measurements from imaging of the retinal nerve fibre layer and optic nerve head, and scores from patient-related outcome measures questionnaires at 24 months, or at the time of a trial endpoint.¹⁹

Because visual field deterioration is more likely at higher intraocular pressures, patients leaving the trial after an endpoint would cause the mean intraocular pressure of those remaining to reduce over time. Therefore, missing data (from patients having reached an endpoint or being lost to follow-up) were imputed with the last observation carried forward (LOCF) method.

Procedures

We did visual field testing, intraocular pressure measurement, and imaging at 11 scheduled visits over 24 months, with clustering of the tests at baseline, 18 months, and 24 months; 16 visual fields test were scheduled over 24 months. We measured vision function through testing of the visual field. The visual field test estimates retinal sensitivity, measured in dB, at 54 locations across the central 24 degrees, one eye at a time; 52 of which are analysed in the instrument software for change over time. A summary measure of vision function is the average loss at all locations: the mean deviation. Criteria for incident damage are based on identification of visual field locations that are repeatedly worse than baseline; these criteria are sensitive and identify change before it is noticed by the patient. Visual field testing was done with the Humphrey Field Analyser Mark II (or II-i) with the Swedish interactive threshold algorithm standard 24-2 programme (Carl Zeiss Meditec, Dublin, CA, USA). We measured visual field deterioration with the Humphrey Field Analyzer II-i Guided Progression Analysis software (version 5.1.1). Two independent glaucoma-fellowship-trained ophthalmologists (Nick Strouthidis [Moorfields Eye Hospital] and Paul Foster [UCL]) confirmed that the deterioration was consistent with open-angle glaucoma on review of the visual fields and a fundus photograph taken at the time that the patient reached the endpoint. For eye-related variables, the values for the eye with worse baseline mean deviations were taken. Detail of other procedures is given in the appendix.

Statistical analysis

At the start of the trial, we decided the sample size based on our outcome at 18 months. However, because recruitment was slower than we expected, we recalculated the sample size in Oct 8, 2008, for an outcome at 24 months. We further revised the sample size in June 3, 2009, because of a greater than anticipated attrition rate. We established the final sample size (516 participants) to have 90% power with a two-sided error ($\alpha=0.05$) to detect a difference between 24% and 11% in incident visual field deterioration in 24 months' follow-up, allowing for a 25% loss to follow-up over the study period.

We analysed all patients in the treatment group to which they were randomly assigned with all available data up to the point of withdrawal. If no data were available for any post-baseline assessment, we excluded patients from the analysis. We censored data from patients undergoing any ocular surgery at the last visit before surgery and included these patients in the loss to follow-up numbers.

We used survival analysis to compare the differences in time from baseline to the event of confirmed deterioration between treatment groups. We estimated treatment effect as hazard ratios (HR) with 95% CIs computed by a Cox proportional hazards model that included terms, prespecified in the statistical analysis plan, for treatment, baseline covariates (age at baseline, race [white or

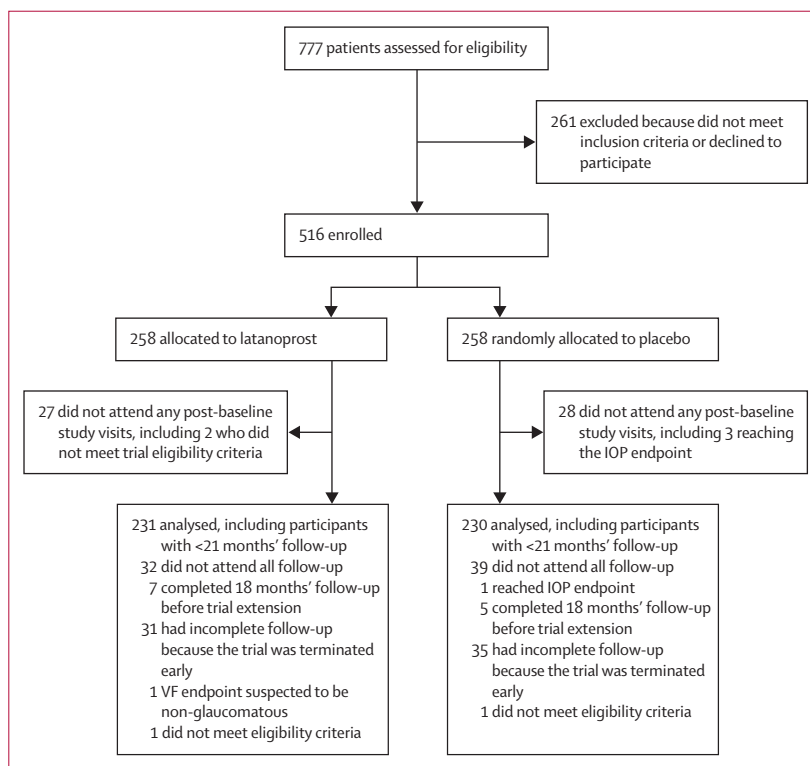


Figure 1: Study profile

IOP=intraocular pressure. VF=visual field. Four patients who did not fulfil the eligibility criteria were randomised. Two did not attend any post-baseline visits (both in the latanoprost group). Of the remaining two, one was analysed in the latanoprost group and one in the placebo group.

	Placebo group (n=258)	Latanoprost group (n=258)
Centre		
Moorfields Eye Hospital	45 (17%)	46 (18%)
Aberdeen Royal Infirmary	21 (8%)	21 (8%)
Norfolk and Norwich University Hospital	42 (16%)	41 (16%)
Birmingham Heartlands and Solihull	37 (14%)	37 (14%)
Cheltenham General Hospital	12 (5%)	12 (5%)
Bristol Eye Hospital	13 (5%)	13 (5%)
Sunderland Eye Infirmary	16 (6%)	16 (6%)
Hinchingbrooke Hospital	55 (21%)	54 (21%)
Addenbrooke's Hospital	10 (4%)	11 (4%)
West of England Eye Unit	1 (<1%)	1 (<1%)
Huddersfield Royal Infirmary	6 (2%)	6 (2%)
Family history of glaucoma		
None	175 (68%)	173 (67%)
First-degree relative	82 (32%)	82 (32%)
Other family history	1 (<1%)	1 (<1%)
Unknown	0	2 (1%)
Age (years)		
Mean	66 (10)	65 (11)
20–29	1 (<1%)	1 (<1%)
30–39	2 (1%)	2 (1%)
40–49	17 (7%)	23 (9%)
50–59	56 (22%)	41 (16%)
60–69	80 (31%)	101 (40%)
70–79	84 (33%)	78 (30%)
≥80	18 (7%)	12 (5%)
Sex		
Female	125 (48%)	118 (46%)
Male	133 (52%)	140 (54%)
Education level		
Degree	46 (18%)	50 (19%)
Apprenticeship or certificate	70 (27%)	67 (26%)
Ended at age 18 years	13 (5%)	20 (8%)
Ended at age 16 years	126 (49%)	118 (46%)
Unknown	3 (1%)	3 (1%)

(Table 1 continues in next column)

non-white], sex, baseline intraocular pressure, baseline mean deviation, blood pressure, refractive error, axial length, and central corneal thickness), and study centre. For patients who had no post-baseline data, we developed a regression model with the remaining data and used this to estimate times to progression. The Cox model was re-run with the imputed values for the patients with no post-baseline data and estimates compared with the available case model.

We investigated reasons for loss to follow-up with logistical regression of covariates (including treatment group, intraocular pressure, baseline mean deviation, age, sex, and ethnic origin) on an indicator of loss. Summary measurements for continuous, normally distributed, outcome values were differences in means

	Placebo group (n=258)	Latanoprost group (n=258)
(Continued from previous column)		
Ethnic origin		
White	230 (89%)	235 (91%)
Black	17 (7%)	10 (4%)
Asian	7 (3%)	9 (4%)
Other	1 (<1%)	2 (<1%)
Unknown	3 (1%)	2 (<1%)
Systolic blood pressure		
Mean (mm Hg)	135.7 (20.2)	135.5 (19.4)
Missing data*	22 (9%)	21 (8%)
Diastolic blood pressure		
Mean (mm Hg)	80.3 (11.0)	81.1 (10.5)
Missing data*	22 (9%)	21 (8%)
Hypertension		
Receiving treatment	102 (40%)	105 (41%)
Manifest hypertension (BP>140/90 mm Hg)	118 (46%)	110 (43%)
Medical history		
Heart attack	15 (6%)	13 (5%)
Bronchitis or emphysema	15 (6%)	16 (6%)
Asthma or wheezing	30 (12%)	30 (12%)
General arteriosclerosis (stroke, angina, and claudication)	13 (5%)	25 (10%)
Diabetes	25 (10%)	29 (11%)
Concomitant neurological disease (Parkinson's disease, Alzheimer's disease, multiple sclerosis, or deafness)	32 (12%)	33 (13%)
Migraine	50 (19%)	51 (20%)
Peripheral vasospasm	94 (36%)	88 (34%)
Medication use		
Corticosteroids (including inhalers)	17 (7%)	28 (11%)
Statins	65 (25%)	75 (29%)
Other	157 (61%)	151 (59%)

Data are n (%) or mean (SD). BP=blood pressure. *Data are missing for participants who did not attend the first post-allocation visit.

Table 1: Baseline characteristics

and corresponding 95% CIs. For non-parametric equivalents, we used non-normally distributed outcome measures. For categorical variables, we used a Pearson's χ^2 or Fisher's exact test. We used survival analysis and linear regression to assess glaucoma severity as a risk for visual field deterioration. We used linear regression to assess imaging outcomes for evidence of deterioration before a confirmed visual field endpoint in patients with baseline mean deviation lower than -10 dB (appendix). All statistical tests used a two-sided p value of 0.05. We did statistical analyses with Stata (version 12). This trial is registered, number ISRCTN96423140.

Role of the funding source

The funders had no input into the design, conduct, data collection, analysis, result interpretation, or reporting of

	Placebo group (n=258)	Latanoprost group (n=258)
Eyes eligible for trial		
Both eyes	136 (53%)	129 (50%)
Right eye only	62 (24%)	68 (26%)
Left eye only	59 (23%)	58 (22%)
Neither	1 (<1%)	3 (1%)
Refractive error		
Mean (D)	-0.7 (3.1)	-0.7 (3%)
Less than -1 D	80 (31%)	87 (34%)
-1 to 1 D	118 (46%)	110 (43%)
More than 1 D	60 (23%)	60 (23%)
Unknown	0	1 (<1%)
Best-corrected visual acuity		
Mean	0.95 (0.24)	0.94 (0.22)
0.5 to 0.6	91 (36%)	81 (31%)
1.0 and better	165 (64%)	177 (69%)
Missing data*	2 (1%)	0
Axial length		
Mean (mm)	24.1 (1.27)	24.1 (1.31)
Missing data*	31 (12%)	29 (11%)
CCT		
Mean (mm)	543.6 (33.3)	539.3 (33.9)
Missing data*	27 (11%)	25 (10%)
SAP MD		
Better eye		
Mean (dB)	-1.6 (1.9)	-1.4 (1.9)
Median (dB)	-1.4 (-2.6 to -1.3)	-1.2 (-2.1 to -0.1)
Worse eye		
Mean (dB)	-4.4 (3.4)	-4.3 (3.4)
Median (dB)	-3.3 (-6.0 to -2.0)	-3.3 (-5.3 to -2.1)
GAT IOP, mm Hg		
Mean	20.1 (4.8)	19.6 (4.6)
<15	29 (11%)	36 (14%)
15-19	102 (40%)	107 (42%)
20-24	83 (32%)	80 (31%)
25-29	37 (14%)	29 (11%)
≥30	7 (3%)	6 (2%)
Any iridotrabecular contact		
Yes	25 (10%)	22 (9%)
No	232 (90%)	236 (92%)
Unknown	1 (<1%)	0

(Table 2 continues in next column)

	Placebo group (n=258)	Latanoprost group (n=258)
(Continued from previous column)		
Van Herick grade		
0%	2 (1%)	3 (1%)
≥5%	0	1 (<1%)
≥15%	7 (3%)	7 (3%)
≥25%	64 (25%)	47 (18%)
≥40%	185 (72%)	200 (78%)
Unknown	6 (2%)	8 (3%)
Any peripheral anterior synechiae		
Yes	2 (1%)	1 (1%)
No	254 (98%)	257 (99%)
Unknown	2 (1%)	0
Trabecular pigment density		
0	48 (19%)	45 (17%)
1	156 (61%)	158 (61%)
2	45 (17%)	45 (17%)
3	5 (2%)	10 (4%)
Unknown	4 (2%)	0
Pseudoexfoliation		
0	250 (97%)	255 (99%)
1	0	1 (<1%)
2	1 (<1%)	0
Unknown	7 (3%)	2 (1%)
LOCS lens grading-N		
N ≥1	139 (54%)	137 (54%)
N <1	113 (44%)	118 (46%)
Unknown	6 (2%)	3 (1%)
LOCS lens grading-C		
C ≥2	12 (5%)	10 (3.8)
C <2	240 (93%)	245 (95.0)
Unknown	6 (2%)	3 (1.2)
LOCS lens grading-P		
P ≥1	20 (8%)	21 (8%)
P <1	232 (90%)	234 (91%)
Unknown	6 (2%)	3 (1%)

Data are n (%) or mean (SD) and median (IQR). Values given are for pre-allocation or post-allocation visit 1. Where relevant, values for the eye with the worse visual field mean deviation are given. CCT=central corneal thickness. SAP MD=standard automated perimetry mean deviation. GAT IOP=Goldmann applanation tonometry intraocular pressure. D=dioptries. LOCS=lens opacity classification system. N=nuclear cataract. C=cortical cataract. P=posterior subcapsular cataract. *Data are missing for participants who did not attend the first post-allocation visit.

Table 2: Baseline characteristics of the latanoprost-treated versus placebo-treated eyes of patients

the study. Some of the authors are employed by the sponsor organisation (Moorfields Eye Hospital). The organisation itself had no input. The corresponding author has full access to all data and had final responsibility to submit for publication.

Results

Between Dec 1, 2006, and March 16, 2010, we enrolled 516 patients (first randomisation Feb 1, 2007; figure 1). 55 patients did not attend any post-baseline visits (27 from

the latanoprost group and 28 from the placebo group) and, therefore, provided no outcome data to analyse. Four patients were found to not fulfil eligibility criteria after randomisation, but the two with post-baseline data were included in the analysis. We analysed data for the primary trial outcome for 461 patients (figure 1).

Table 1 shows baseline characteristics of participants and table 2 shows eye-related parameters. Treatment

groups were mostly similar; arteriosclerosis was more common in patients given latanoprost than in controls (table 1). Mean intraocular pressure at baseline seemed slightly higher in the placebo group than in the latanoprost group (table 1).

Within 24 months, 94 participants had visual field deterioration consistent with glaucomatous progression in 461 patients with post-baseline data (231 in the latanoprost group and 230 in the placebo group). 59 (25.6%; 95% CI 20.1–31.8) patients in the placebo group reached the deterioration endpoint at 24 months compared with 35 (15.2%; 10.8–20.4) in the latanoprost group ($p=0.006$). In one additional participant, an endpoint was deemed potentially to be due to a non-glaucomatous process. The visual field deterioration

endpoint was reached in both eyes of ten participants. Based on the 94 patients with visual field deterioration events during the 24 month observation period, time to first deterioration was significantly longer in the latanoprost group than in the placebo group (adjusted HR 0.44, 95% CI 0.28–0.69; $p=0.0003$; figure 2). Treatment differences were evident at 18 months (0.43; 0.26–0.71; $p=0.001$), and 12 months (0.47; 0.23–0.95; $p=0.035$). 193 (75%) participants in the placebo group and 210 (81%) in the latanoprost group were taking trial drops and under observation or had reached an endpoint at 12 months. In the model with imputation, the primary endpoint HR was 0.43 (95% CI 0.26–0.69; $p=0.0005$).

At the first visit after treatment allocation, mean intraocular pressure reduction from baseline was 5.0 mm Hg (SD 3.6) in the latanoprost group and 1.4 mm Hg (3.1) in the placebo group. At 24 months, the mean intraocular pressure reduction from baseline was 4.0 mm Hg (3.4) in the latanoprost group and 1.3 mm Hg (3.6) in the placebo group (figure 3A). After we applied the LOCF adjustment, the intraocular pressure reduction at 24 months from baseline was 3.8 mm Hg (4.0) in the latanoprost group and 0.9 mm Hg (3.8) in the placebo group (figure 3B).

In participants reaching a visual field endpoint, the mean change in mean deviation was -1.6 dB (IQR -0.6 to -2.6 dB; figure 4). Mean change in visual acuity (decimal) at last visit from baseline was $+0.01$ for eyes with visual field progression and -0.02 for eyes without visual field progression (Wilcoxon rank-sum test for difference $p=0.3$). Change from baseline visual acuity was -0.01 in the placebo group and -0.02 in the latanoprost group (Wilcoxon rank-sum test for difference $p=0.9$).

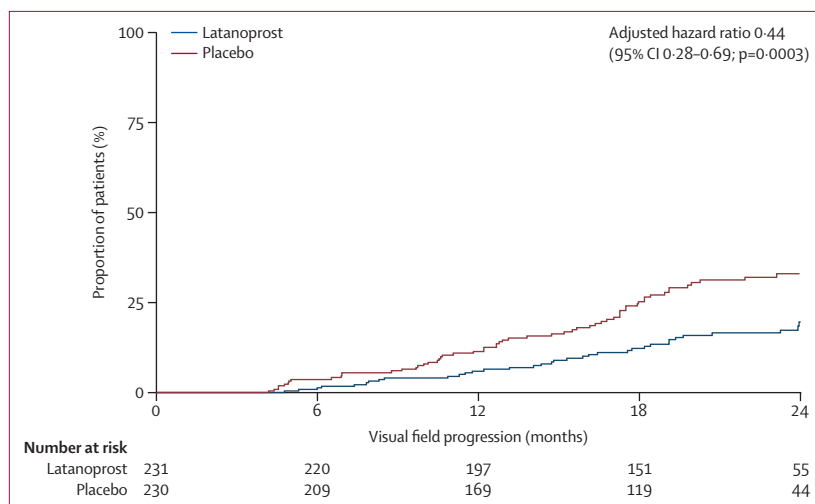


Figure 2: Kaplan-Meier failure estimates for visual field progression

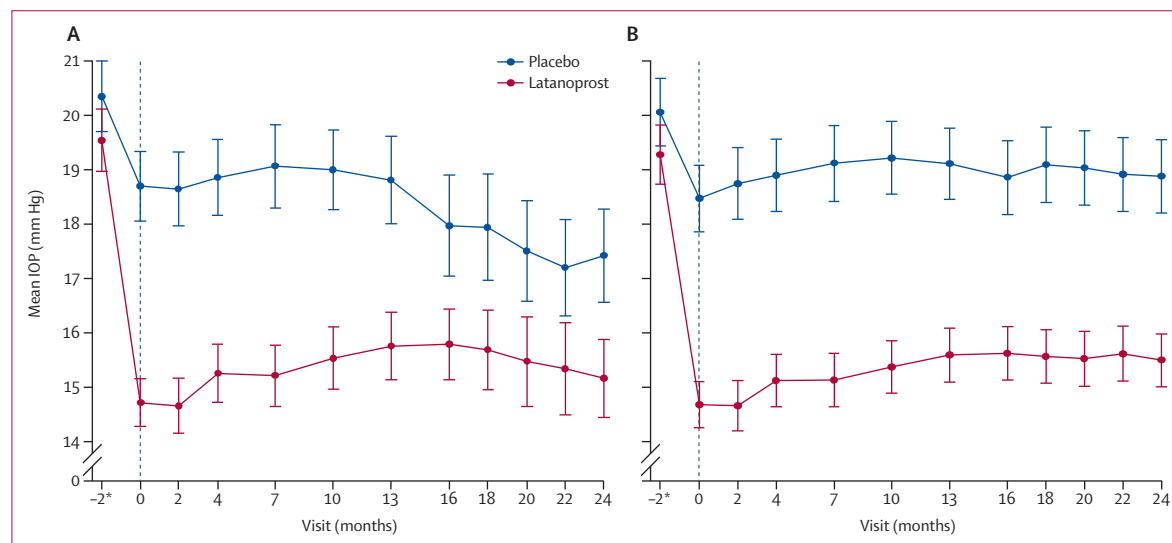


Figure 3: IOP over trial period

IOP in patients under follow-up (A) and in all patients with last observation carried forward for patients no longer under follow-up (B). IOP is given for the eye with the worst visual field MD. Error bars represent the 95% CI around the mean. IOP=intraocular pressure. *Baseline visit at -6 weeks, excluding those who did not attend at 0 months.

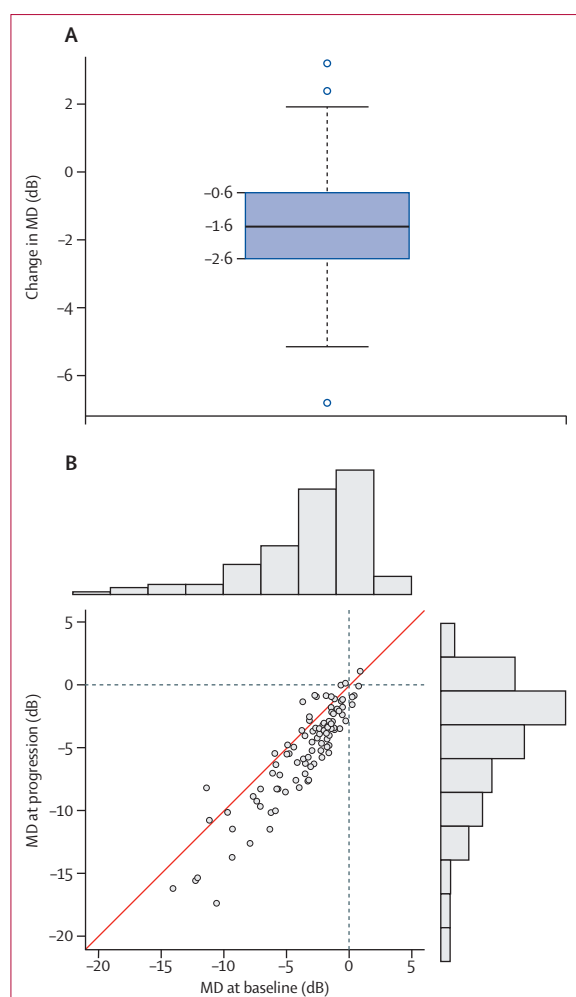


Figure 4: Change from baseline in visual field MD at the time of the primary end point

(A) Shows median (horizontal bar), IQR (shaded box), 1.5-times the IQR (whiskers), and outliers (open circles). (B) Scatterplot of baseline MD versus MD at endpoint. MD=mean deviation.

27 (10%) patients in the latanoprost group and 28 (11%) participants in the placebo group did not attend any post-baseline appointments. We explored the following associations for patients lost to follow-up (those with no post-baseline visits): age, sex, baseline intraocular pressure, baseline visual field loss, ethnic origin, and treatment group. There were no associations at the $p < 0.05$ level.

A further 32 (12%) patients in the latanoprost group and 39 (15%) in the placebo group had shorter than 21 months' follow-up because of failure to attend follow-ups or they had an intraocular pressure endpoint (figure 1). Of those lost by reason of ocular comorbidity, eight underwent cataract surgery (five from the placebo group), seven of which were within 7 months of the baseline visit (table 3, table 4). Of the 3750 scheduled appointments before planned trial exit or loss to follow-up, 63 (2%) were missed; 32 by patients in the placebo group and 31 by those in the

	Placebo group (n=230)		Latanoprost group (n=231)	
	Number of events	n (%)	Number of events	n (%)
Mild				
Total mild events	76	39 (17%)	76	40 (17%)
Ocular				
Unscheduled drop holiday	2	2 (1%)	2	2 (1%)
Ocular discomfort*	16	14 (6%)	16	13 (6%)
Conjunctivitis†	6	6 (3%)	6	6 (3%)
Adnexal‡	2	1 (1%)	2	2 (1%)
Subconjunctival haemorrhage	3	2 (1%)	3	3 (1%)
Vision alteration§	11	12 (6%)	11	8 (3%)
Optic disc haemorrhage	7	6 (4%)	7	6 (3%)
Non-ocular				
General medical¶	29	15 (11%)	29	22 (10%)
Moderate				
Total moderate events	13	9 (4%)	8	8 (3%)
Ocular				
Conjunctivitis	0	0	2	2 (1%)
Vision alteration	3	2 (1%)	2	2 (1%)
Non-ocular				
General medical	10	7 (4%)	4	4 (2%)
Serious				
Total serious events	7	7 (3%)	9	8 (3%)
Death (unknown cause)	0	0	2	2 (1%)
Cancer diagnosis	4	2 (2%)	2	2 (1%)
Cerebrovascular accident	1	1 (<1%)	4	3 (2%)
Myocardial infarction	2	1 (1%)	1	1 (<1%)
Other (surgery)	2	2 (1%)	0	0

*Includes dry eyes and blepharitis. †Includes infective and allergic conjunctivitis. ‡Includes blocked nasolacrimal duct and eyelid papillae. §Includes cataract, age-related macular degeneration, and diabetic maculopathy. ¶General medical (mild) includes respiratory infection, injury, arthritis, and suspected cancer. ||General medical (moderate) includes inpatient surgery and other hospital admissions.

Table 3: Adverse events

latanoprost group. 79 participants had incomplete follow-up from early trial termination or had completed 18 months' follow-up before the extension of the observation period (figure 1, appendix).

An intraocular pressure safety endpoint was reached in six participants, two of whom simultaneously reached a visual field endpoint. No patient reached a visual acuity reduction endpoint. 192 adverse events (99 in patients allocated to placebo and 93 in patients allocated to latanoprost) were reported in 98 participants (50 participants in the latanoprost group and 48 in the placebo group; table 3). 13 of 153 mild adverse events and one of 21 moderate adverse events were thought to be possibly related to study drugs (four in the placebo group, ten in the latanoprost group). 18 serious AEs were reported (nine in the placebo group and nine in the latanoprost group), none attributed to the study drug. Seven patients withdrew because of a possible adverse reaction to study drug (table 4): local allergy (in two patients), drop intolerance (in three), diarrhoea (in one), and asthma (in one).

	Latanoprost group (n=58)	Placebo group (n=69)
Adverse reaction to study drug	4 (3%)	3 (2%)
Ill health	10 (8%)	22 (17%)
Death	5 (4%)	2 (2%)
Ocular comorbidity*	6 (5%)	5 (4%)
Intraocular pressure endpoint	0 (0%)	4 (3%)
Unknown or other	33 (26%)	33 (26%)

Data are n (% of those with less than 21 months follow-up; total 127). *Included cataract, angle closure, or uveitis.

Table 4: Reasons for follow-up of less than 21 months

Panel: Research in context

Systematic review

On Nov 10, 2013, we searched the Cochrane Eyes and Vision database with the subtopics Glaucoma–Glaucoma, open angle–Treatment–Topical therapy. The search identified two relevant reviews about medical treatment for open-angle glaucoma,^{7,23} but no placebo-controlled trials assessing the benefit of topical intraocular pressure-lowering drugs on preservation of visual function. Notably, no evidence was available for the vision-preserving effects of intraocular pressure-lowering by prostaglandin analogues—the most commonly-prescribed class of drug for glaucoma. We searched PubMed for papers published from May 1, 2007, to Nov 10, 2013, with the MeSH terms “glaucoma”, “clinical trial”, and “visual field”. This search identified 76 publications, including one additional open-label medical treatment study¹⁰ with vision function as a primary outcome that was not already identified in the Cochrane reviews. We assessed trial quality on the basis of four metrics: allocation concealment, performance bias, detection bias, and attrition bias.

Interpretation

To our knowledge, the United Kingdom Glaucoma Treatment Study (UKGTS) is the first randomised, triple-masked, placebo-controlled trial to assess the benefit of topical medical treatment (eye drops) for reduction of loss of vision in patients with open-angle glaucoma. Our findings provide strong evidence for the vision-preserving benefit of lowering of intraocular pressure, supporting evidence from previous randomised trials that were not masked or placebo-controlled. The study also provides evidence of the vision-preserving benefits of topical prostaglandin analogues. The trial design meant a fairly short observation period was needed to show treatment effects on vision, with the difference between treatment groups evident at just 12 months compared with typical observation periods of roughly 5 years in previous trials. The short trial duration will have a major beneficial effect on development and assessment of new treatments, increasing the likelihood of these treatments being made available for patient benefit.

Discussion

Systematic reviews of treatment for glaucoma have reported no placebo-controlled trials in patients with open-angle glaucoma with visual function as the outcome (panel).^{9,23} To our knowledge, no evidence exists for a protective effect on vision for the most frequently prescribed class of drugs to lower intraocular pressure—prostaglandin analogues.⁷ To our knowledge, UKGTS is the first placebo-controlled trial to show visual field preservation through lowering of intraocular pressure with topical drugs in patients with open-angle glaucoma and to show the visual-field-preserving effect of latanoprost, the drug most frequently used in

high-income countries. Previous studies, such as the EMGT⁹ and the Collaborative Normal Tension Glaucoma Study,¹² have assessed the outcome of combined treatments to lower intraocular pressure. Our placebo-controlled trial is of clinical relevance in view of the results of a recent trial by Krupin and colleagues suggesting very different vision-preserving action of two drugs with similar intraocular-pressure-lowering efficacy.¹¹ The effect size in the UKGTS was large, with an adjusted HR of 0.44 (95% CI 0.28–0.69), associated with initial intraocular pressure-lowering of 5.0 mm Hg (SD 3.6) in the latanoprost group and 1.4 mm Hg (3.1) in the placebo group. The initial intraocular pressure reduction from baseline (5.0 mm Hg of 19.6 mm Hg; 26%) with latanoprost in our trial was lower than the 31% (peak) and 28% (trough) reduction from baseline reported in a meta-analysis by van der Valk and colleagues.²⁴ However, in their meta-analysis, both the baseline peak (25.5 mm Hg) and trough (24.3 mm Hg) levels were higher than was the baseline pressure in the UKGTS (19.6 mm Hg). The intraocular pressure reduction at 24 months (3.8 mm Hg) is in line with data obtained for cohorts with lower baseline pressure—eg, 3.2 mm Hg from 17.6 mm Hg²⁵ and 3.9 mm Hg from 18.8 mm Hg.²⁶ The reduction in intraocular pressure lessened a little over the 24 months; in the LOCF analysis, the intraocular-pressure reduction compared with baseline was 3.8 mm Hg in the latanoprost group and 0.9 mm Hg in the placebo group (figure 3B). The pattern of intraocular-pressure reduction, with a strong initial response that diminished after 6 months and then stabilised, has been reported previously.²⁵ The pressure reduction in the placebo group (figure 3B)—which was greater at the first post-allocation visit (1.4 mm Hg) than at the visit at 24 months (0.9 mm Hg)—might be a regression-to-the-mean effect due to clinician behaviour (with the desire to recruit participants into a trial, a clinician might be more likely to accept borderline clinical findings as glaucoma when the intraocular pressure reading is high and, after randomisation and start of drops, might have a greater expectation of lower intraocular pressure at the first post-allocation visit), or might be a true hypotensive effect of latanoprost vehicle eye drops or a true placebo effect.

Only two previous trials have been published of medical (non-incisional) treatment for open-angle glaucoma with an untreated control group and vision function as an outcome—the study by Holmin and colleagues⁸ and the EMGT.⁹ Neither study was placebo-controlled or masked, although both had an objective (visual field) outcome. The study by Holmin and colleagues⁸ was very small (16 patients enrolled). Previous trials of open-angle glaucoma with visual field deterioration as an outcome have used widely differing criteria to identify deterioration and have studied differing clinical populations than each other,^{9,12,15,16} whereas we chose the recruitment criteria and main

outcome of the UKGTS to be similar to those of the EMGT to allow comparison and meta-analysis of results. The outcome criterion was established from the glaucoma change probability maps, which are based on the pattern deviation, limiting the effect of homogeneous reduction in differential light sensitivity seen with cataract.⁹ The observation period of the trial was short (24 months) and little change in lens opacity would be expected; as shown by the stability of the visual acuity over the duration of this study.

From our estimation of incident progression from the survival curves (figure 2), a visual field endpoint was reached by 24 months in 34% of participants in the untreated group of the UKGTS and 25% in the untreated group of the EMGT, versus in 20% of participants in the treated group of the UKGTS and 11% in the treated group of the EMGT. Since baseline intraocular pressure (19.9 mm Hg in UKGTS, 20.6 mm Hg in EMGT) and participant age (66 years in UKGTS, 68 years in EMGT) were similar,^{20,21} the higher incident progression in the UKGTS might have been caused by the more sensitive criterion to identify progression. The relative sensitivity of the endpoint criteria can be judged from the median change in visual field mean deviation between baseline examination and the time at which deterioration was confirmed: -1.6 dB for the UKGTS criterion (figure 4) and -1.9 dB for the EMGT criterion.²⁷ Incident progression was reduced by 41% in the treated group of UKGTS, compared with a 58% reduction in the EMGT; this finding is consistent with the 16% smaller intraocular pressure-lowering treatment effect in the UKGTS (-3.8 mm Hg vs -4.5 mm Hg in the EMGT).

Strengths of the UKGTS trial (and EMGT trial) are that newly diagnosed, previously untreated participants were studied, so that the results are free of influence from previous therapeutic interventions and the natural history of open-angle glaucoma can be studied in the untreated patients. Because consecutive new patients were assessed and recruited for the UKGTS trial, the population studied was representative of the target population considered for treatment and on which the trial results will be applied.

The UKGTS has the shortest observation period of any glaucoma trial with a vision function outcome,^{9-13,15,16} with a statistically significant difference between treatment groups evident at only 12 months, as well as at the planned 24 month analysis timepoint. However, because the significance of the difference in proportions surviving in the EMGT was $p=0.004$ after 48 months' observation,⁹ the difference between treatment groups in the EMGT was probably significant over a much shorter observation period than was reported. The short observation period needed to observe a treatment effect can bring many benefits, speeding up novel drug development with consequent cost reduction and thereby increasing the likelihood of bringing new drugs to patients. The short observation period was achieved by adopting a sensitive

change-from-baseline event criterion to identify visual field deterioration, frequent visual field tests, and a sufficiently large sample size. Also, the UKGTS design included additional features that might further reduce study duration and sample size. We aimed to improve the accuracy and precision of the rate (speed) of progression by including the clustering of tests at the beginning and end of the observation period¹⁷ and quantitative imaging of the retinal nerve fibre layer and optic nerve head;¹⁸ the analysis of these secondary outcomes will be reported elsewhere.

Because two-thirds of patients in the placebo group had no detectable deterioration within 24 months, and the small amount of change needed for an endpoint occurred in just one eye of almost 90% of participants with data, the questions arises as to whether some patients with glaucoma, particularly those with less visual field loss at baseline and those at lower risk of progression,^{28,29} could be monitored without treatment for a period. Investigators have previously suggested initial careful observation without treatment in patients with open-angle glaucoma⁹ and normal tension glaucoma.³⁰ Because deterioration patterns are difficult to predict,³¹ an observation period would be advantageous to identify patients who might not need treatment, thereby avoiding the unnecessary burden of treatment for such patients. The rate of progression of visual field loss might change over extended observation periods, and so regular reassessments of the rate of progression would be advisable.

A potential limitation of the UKGTS was the relatively high loss to (or incomplete) follow-up, which can reduce the generalisability of the results. However, individuals lost to follow-up were generally similar to those remaining in the trial. In addition, participant ascertainment was not population-based, but based on referral from primary care (community optometry practice); however, the participant characteristics in the UKGTS²⁰ were strikingly similar to those in the EMGT, in which ascertainment was largely based on population screening.²¹ UKGTS participants were predominantly white (about 90%), which might also reduce generalisability of our findings to some subpopulations in the UK or other countries who might exhibit greater susceptibility to vision loss.^{32,33} Furthermore, individuals with advanced open-angle glaucoma were excluded so that the results of the trial only apply to patients with mild to moderate glaucoma. Subsequent publications will address the effect of treatment with respect to baseline intraocular pressure, glaucoma stage, participant age, and other risk factors.

Contributors

DFG-H, DPC, and CB conceived of and designed the trial and RPW guided the set-up and conduct of the trial. DFG-H was the chief investigator for the trial and had oversight of the trial throughout. GL and AS were the trial physicians and did the day-to-day running of the study. FA was the trial coordinator. ETW was the chief technician. TGZ chaired the steering committee. GL, AS, NA, AA-B, RRB, DCB, IAC, JPD, SGF, KRM, AIM, AN, and PGS recruited patients and reported

corresponding data. KS assisted with data preparation and analysis; CB, KP, RAR, and WX were the trial statisticians and did the final statistical analyses of the results. DFG-H led the interpretation of the data and writing of the manuscript, assisted by TAH. All authors had input into the data interpretation and preparation of the final report for publication.

Declaration of interests

DFG-H has received unrestricted research funding from Allergan and Pfizer, equipment loans from Carl Zeiss Meditec, Heidelberg Engineering, and Optovue; has had advisory roles (compensated) with Alcon, Alimera, Allergan, Bausch & Lomb, Forsight, GlaxoSmithKline, Merck, and Quark; and honoraria for lecturing from Allergan, Bausch & Lomb, and Merck. DPC has received unrestricted research funding from Allergan, Pfizer, and Merck, and honoraria for lecturing from Allergan and Merck. RRB has received unrestricted research funding from Allergan and Heidelberg Engineering, and equipment loans from Heidelberg Engineering. DCB has received research funding from the Wellcome Research Foundation, Pfizer, National Institute for Health Research, the Medical Research Council, Fight For Sight, The Edith Murphy Foundation, and The Humane Society; payments to The Norwich Glaucoma Research Fund for involvement in commercial trials from Allergan and Promedior; and honoraria for lecturing from Santen, Merck, and Alcon. IAC has received research funding from Allergan, Alcon, and Merck Worldwide (MSD), travel funding from Alcon, Allergan, and MSD; has had advisory roles with Alcon and Allergan; and lecturing honoraria from Allergan. TAH has received honoraria from Allergan for consultancy on education programmes. AIM has received compensation for lecturing, travel expenses, and consulting from Pfizer, Allergan, Alcon, MSD, and Heidelberg Engineering. His institution has received research funding from Pfizer, Allergan and Novartis. PGS has received honoraria for lecturing from Allergan. TGZ has had advisory roles (compensated) with Pfizer and Merck and honoraria for lecturing from Merck and Th  a. CB, GL, FA, NA, AA-B, JPD, SGF, KRM, KP, RAR, AS, KS, ETW, RPW, and WX declare no competing interests.

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